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TITLE: Inherited Susceptibility to Breast Cancer in Healthy Women:
Mutation in Breast Cancer Genes, Immune Surveillance, and
Psychological Distress

PRINCIPAL INVESTIGATOR: Dana H. Bovbjerg, Ph.D.

CONTRACTING ORGANIZATION: Mount Sinai School of Medicine
New York, New York 10029-6574

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INTRODUCTION:

Modifying genes and/or environmental factors are likely to have a major impact on the risk of breast cancer in women carrying mutations in primary breast cancer susceptibility genes (BRCA1/BRCA2) (Antoniou et al., 2002; Couch, 2004). Variability in the penetrance of mutations in the primary susceptibility genes has been clearly demonstrated, however, we as yet know little about the mechanisms responsible for such variability (Dite et al., 2000; Antoniou et al., 2002; Couch, 2004). To date, most research has focused on hormonal/reproductive variables that have been shown to be risk factors for the development of breast cancer independent of familial risk for the disease (DeJong et al., 2002; Martin & Weber, 2000). Some risk factors for breast cancer, however, are likely to have an impact only in conjunction with mutations in primary susceptibility genes (Antoniou et al., 2002; Petro, 2002; Couch, 2004). Such modifying risk factors might not be revealed in standard epidemiological studies, but would emerge when examined in conjunction with testing for primary susceptibility genes (DeJong et al., 2002).

One potential modifying risk factor that has yet to receive much research attention is deficits in immune surveillance mechanisms, although there is increasing evidence of effects of both innate (e.g., natural killer cell activity) and acquired immunity (e.g., cytotoxic T cells) on cancer risk in animal models and humans (Dunn GP, Old LJ, Schreiber RD, 2004). Although there have been a number of reports of reduced levels of natural killer cell activity (NKCA) in women at familial risk of cancer (Bovbjerg & Valdimarsdottir, 2001), the possible relationships between deficits in NKCA and BRCA have not yet been investigated. One major challenge to the examination of such relationships is that NKCA is particularly responsive to psychological stress, (Segerstrom & Miller, 2004) and women at familial risk for breast cancer are stressed (Bovbjerg & Valdimarsdottir, 2001). Recent studies, from our group and others, have not only documented chronically heightened levels of self-reported distress (e.g., Lindberg & Wellisch, 2004; Schnur et al., 2004; Kim et al., in press), but also deficits in cognitive processing of cancer-related information (Erblich et al., 2003), and an increased psychobiological reactivity to acute stressors under experimental conditions (Valdimarsdottir et al., 2002; Gold et al., 2003) and in the course of daily life (James et al., 2004; Dettenborn et al., in press). Recognizing the potential psychological, behavioral and biological significance of stress, intervention studies to reduce stress in these women are increasingly found in the literature (e.g., Bowen et al., 2004; McInerney-Leo et al., 2004).

The purpose of the ongoing research supported by this IDEA grant award is to test the possibility that differences in the strength of immune surveillance mechanisms against cancer (operationally defined as natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. The first aim of this study is to investigate two possible explanations for variability in NKCA (Bovbjerg & Valdimarsdottir, 2001): 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. The second aim is to examine the possibility that inherited deficits in immune surveillance may be independently associated with familial risk of breast cancer (Bovbjerg & Valdimarsdottir, 2001).

The study "piggy-backs" on other ongoing studies involving familial risk, genetic counseling, and breast cancer gene testing (BRCA1, BRCA2) at Mount Sinai Medical Center under the direction of Co-Investigators on this proposal. These "parent" studies, which provide the infrastructure and funding necessary for recruitment, assessment, genetic counseling, and BRCA testing, are the source of potential participants for the present study. The participants in the present study

are recruited to form three Study Groups (N=80/group) of comparable age for the research: 1) The Mutation-Positive Family History Group (Mut+Hist+) includes women whose family histories of cancer indicate a relative risk ≥ 1.5 for breast cancer and who carry a mutation in BRCA1 or BRCA2; 2) The Mutation-Negative Risk Family History Group (Mut-Hist+) includes women with comparable family histories, who do not carry mutations; 3) The Normal Risk Group (Mut-Hist-) includes women without family histories of cancer who do not carry mutations. Study participants are asked to complete psychological assessments (e.g., standardized self-report measures) in conjunction with their involvement with the parent studies that fund the genetic testing (e.g., once prior to their genetic counseling session/blood draw and twice after notification). To reduce participant burden and avoid compromising the parent studies, blood samples for the assessment of NKCA are also collected in conjunction with the women's involvement in the parent studies, by collecting additional samples when the women are already providing a sample for genetic testing. In the context of the requirements of the parent studies, it has not been feasible to collect blood samples for the two follow-up NK cell assessments originally proposed for this study, as psychological data is collected by telephone. Consistent with scheduling exigencies, NKCA is concurrently assessed in samples from women in each group by personnel "blind" to group status.

BODY:

We have not yet analyzed data from this study, as our intended sample sizes have yet to be met. In the past year recruitment was slowed by a 3-month hiatus in recruitment by one of the parent studies on which this study depends. Nonetheless, over the past year psychological assessments of stress associated with familial risk and genetic testing have been conducted with 40 women (Mut+Hist+ n=16; Mut-Hist+ n=21; Mut-Hist- n=3). Of those 40 women, 35 have completed two assessments, eight have completed all three assessments (20 women are not yet due for their second or third assessment yet). Over the entire grant period a total of 224 women have completed psychological assessments (Mut+Hist+ n=70; Mut-Hist+ n=72; Mut-Hist- n= 69). Over the past year, NKCA has been assessed in blood samples from 25 women (Mut+Hist+ n=10; Mut-Hist+ n=12; Mut-Hist- n=3). Over the entire grant period NK cell activity has been assessed in a total of 112 women (Mut+Hist+ n=34; Mut-Hist+ n=38; Mut-Hist- n= 40).

Our progress according to the original Statement of Work is detailed below:

Months 1-3: Preparation for first wave of subjects. Preparation of psychosocial questionnaires and immune assessments. Data base established.

Completed.

Months 4-11: First wave of subjects completes assessments. Data entry and initial analysis.

Completed. In the October 2002 Annual Report to the DOD, we proposed to reduce our sample size to 240 total, 80 per group. Thus, we have completed psychosocial and immune assessments on the first wave of 80 subjects.

Months 12-13: Complete data entry of first wave. Prepare annual report. Prepare for second wave of subjects.

Completed.

Months 14-21: Second wave of subjects completes assessments. Data entry and analyses continues.

Completed. In the 2003 Annual Report to the DOD, we proposed to reduce our sample size for immune assessments to 140, while the sample size for psychosocial assessments remains the same. Thus, we have completed psychosocial and immune assessments on the second wave of subjects.

Month 22: Complete data entry of first wave. Prepare annual report. Prepare for second wave of subjects.

Completed.

Months 23-30: Third wave of subjects completes assessments. Data entry and analyses continues.

Ongoing.

Months 31-36: Complete data entry for third wave. Complete empiric risk determination. Verify study data. Conduct literature review of relevant articles. Meet with research team to review results. Complete statistical analyses. Write manuscripts; prepare graphics. Complete DOD final report.

Ongoing.

PROPOSAL:

We have requested a final, one-year, no-cost extension of the grant to allow us to address the study aims over the course of the next year. With continued strong referral of potential participants to the study as a result of research and clinical efforts by the current team of Co-investigators, we anticipate that we will complete questionnaire data collection (an additional 16 participants needed for our proposed final $n=240$) and blood collection (an additional 28 participants needed for our proposed final $n=140$) within the next 6-8 months, allowing us 4-6 months to clean, check, and analyze data, as well as to write up results for presentation and publication.

KEY RESEARCH ACCOMPLISHMENTS:

At this point in the research it would be premature to conduct statistical analyses to address the primary study aims, so no results are yet available. However, solid progress continues to be made in recruiting participants to the study and collecting data as proposed in the protocol.

REPORTABLE OUTCOMES:

None at this time.

CONCLUSIONS:

At this point in the research, no results are yet available. If the results of the proposed research are consistent with the hypothesis that deficits in immune surveillance (e.g., as a result of stress) moderate the effects of mutations in primary susceptibility genes, the study could have important implications for the eradication of breast cancer. Such results would raise the possibility that appropriate interventions to reduce stress and increase the activity of immune surveillance mechanisms in women carrying mutations in primary susceptibility genes might delay the onset or prevent the development of breast cancer.

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